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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,897	YUN ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,11-52,57 and 62-71* is/are pending in the application.

4a) Of the above claim(s) *29-40,42-52 and 57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,11-28,41 and 62-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/7/2009 has been entered.

Claims 1 and 65 has been amended and claims 69-71 has been added new. Claims 2, 5-10, 53-56, 58-61 have been cancelled. Claims 1, 3, 4, 11-28, 41, 62-71 are currently pending, claims 29-40, 42-52, 57 are withdrawn and claims 1, 3, 4, 11-28, 41, 62-71 are being examined on the merits herein.

Response to Remarks

Applicants' arguments regarding the rejection of Claims 1, 3, 4, 11-28, 41, 62-68 under 35 U.S.C. 112, first paragraph and rejection of Claims 1, 3, 4, 11-28, 41, 62-68 are rejected under 35 U.S.C. 112, first paragraph have been fully considered and found not to be persuasive. Applicants' arguments are addressed in the Response to Arguments section below. Applicants' arguments regarding the 103(a) rejections have been fully considered and are moot in view of new rejections presented in this action. Applicants' amendments necessitated the modified and new rejections presented in this office action. The search and rejections are done with respect to the election of species made on 3/23/2007 (species propranolol as beta blocker, NSAID as non beta blocker

and aging associated condition and loss of parasympathetic function as sub species).

The action is made non-final.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 11, 12, 26, 27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1-3, 30 of U.S. Patent No. (U.S. 7,149,574) ('574).

Claims 1, 11, 12, 26, 27 of the instant application teaches a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta blocker and with at least one electrode and applying electrical energy to treat conditions like inflammatory conditions,

genitourinary conditions, infectious diseases gastrointestinal conditions, endocrine conditions, orthopedic inflammatory conditions, Th-2 dominant conditions, conditions that cause hypoxia, conditions that cause hypercarbia etc.

Claims 1, 11, 12 and 30 of the patent '574 teach a method of treating a subject for a condition caused by an abnormality in said subject's autonomic nervous system said method comprising electrically modulating at least a portion of said subject's autonomic nervous system and by the use of at least one pharmacological agent such as beta blocker to increase the parasympathetic activity/sympathetic activity ratio to treat conditions like inflammatory conditions, genitourinary conditions, infectious diseases gastrointestinal conditions, endocrine conditions, orthopedic inflammatory conditions, Th-2 dominant conditions, conditions that cause hypoxia, conditions that cause hypercarbia etc.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variation of the patent because both the instant application and the co-pending application teaches a method of treating autonomic nervous system abnormality comprising electrically modulating at least a portion of parasympathetic/sympathetic activity.

Claims 1, 23, 24, 70, 71 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1-3, 6, 7, 9, 10, 11, 43, 44, 59 of U.S. Patent No. (U.S. 7,363,076) ('076).

Claims 1, 23, 24, 70, 71 of the instant application teaches a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising

modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta blocker and with at least one additional agent such as non-beta blocker to treat conditions like conditions that cause hypercarbia etc., hypercarbia, acidosis, academia etc.

Claims 1-3, 6, 7, 9, 10, 11, 43, 44, 59 of the patent '076 teach a method of treating a subject for a condition caused by an abnormality in said subject's autonomic nervous system said method comprising treating a subject with at least one of hypoxia, hypercarbia, acidosis etc administering at least one pharmacological agent including beta blockers, calcium channel blockers etc.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variation of the patent because both the instant application and the co-pending application teaches a method of treating autonomic nervous system abnormality comprising administering at least one pharmacological agent including beta blockers, calcium channel blockers etc modulating at least a portion of parasympathetic/sympathetic activity.

Claims 1, 26, 27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1, 6, 12, 15 and 19 of co-pending application No. 11/060,643.

Claims 1, 26, 27 of the instant application teaches a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta blocker and with at least one

electrode and applying electrical energy to treat conditions like inflammatory conditions, genitourinary conditions, infectious diseases gastrointestinal conditions, endocrine conditions, orthopedic inflammatory conditions, Th-2 dominant conditions, conditions that cause hypoxia, conditions that cause hypercarbia etc.

Claims 1, 6, 12, 15 and 19 of the co-pending application teach a method of treating a subject for a condition comprising electrically modulating at least a portion of said subject's autonomic nervous system to increase the parasympathetic activity/sympathetic activity ratio in a manner effective to treat said subject for said conditions chosen from neurodegenerative conditions, gastrointestinal conditions, skin conditions, Th2 dominant conditions.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the co-pending application teaches a method of treating autonomic nervous system abnormality comprising electrically modulating at least a portion of parasympathetic/sympathetic activity.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3, 70 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1, 9, 22 and 24 of co-pending application No. 10/962,190.

Claims 1, 3, 70 of the instant application teaches a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by

administering an effective amount of at least one beta blocker to treat conditions like inflammatory conditions, genitourinary conditions, infectious diseases gastrointestinal conditions, endocrine conditions, orthopedic inflammatory conditions, Th-2 dominant conditions, conditions that cause hypoxia, conditions that cause hypercarbia etc. and said method further comprises determining said parasympathetic/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system.

Claims 1, 9, 22 and 24 of the co-pending application '190 teach a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system comprising administering at least one aldosterone antagonist or an analogue thereof such as a beta blocker to treat at least one conditions such as; neurodegenerative conditions; neuroinflammatory conditions; orthopedic inflammatory conditions; pulmonary conditions; transplant-related conditions, gastrointestinal conditions; genitourinary conditions; aging associated conditions; neurologic conditions; Th-2 dominant conditions etc.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the co-pending application teaches a method of treating autonomic nervous system abnormality comprising administering an agent such as a beta blocker in modulating at least a portion of parasympathetic/sympathetic activity.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 23, 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1-4, 7-10, 14 and 15 of co-pending application No. 10/917,270.

Claims 1, 23, 24 of the instant application teaches a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta blocker and an additional agent such as non steroidal anti-inflammatory agents (NSAID) to treat conditions including aging associated conditions that include cancer, heart conditions, pulmonary diseases, renal conditions etc

Claims 1-4, 7-10, 14 and 15 of the co-pending application teach a method of treating a subject for autonomic dysfunction comprising administering a pharmacological agent, an autonomic nervous system modulator and an anti-inflammatory agent selected from non-steroidal anti-inflammatory agents and an anti-adrenergic agents such as beta blockers, calcium channel blockers etc to treat conditions that include cardiovascular conditions such as hypertension, sudden adult death syndrome, coronary artery disease, thrombosis etc.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the co-pending application teaches a method of treating autonomic nervous system abnormality comprising administering an agent such as a beta blocker and an additional agent such as NSAID.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3, 4, 11-24, 27, 63-66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1, 2, 4, 6-8, 13-16, 30-50, 55-58, 63, 71-76, 81 of co-pending application No. 10/846, 486.

Claims 1, 3, 4, 11-24, 27, 63-66 of the instant application teaches a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta blocker and an additional agent such as non steroidal anti-inflammatory agents (NSAID) to treat conditions including aging associated conditions that include cancer, heart conditions, pulmonary diseases, renal conditions etc and neurodegenerative conditions; neuroinflammatory conditions; orthopedic inflammatory conditions; pulmonary conditions; transplant-related conditions, gastrointestinal conditions; genitourinary conditions; aging associated conditions; neurologic conditions; Th-2 dominant conditions etc.

1, 2, 4, 6-8, 13-16, 30-50, 55-58, 63, 71-76, 81 of the co-pending application teach a method of treating a subject for autonomic dysfunction comprising administering a pharmacological agent, such as beta blockers to treat conditions that include OB/GYN conditions, inflammatory conditions, neurodegenerative, pulmonary, infectious disease conditions, autoimmune conditions etc.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the co-pending application

teaches a method of treating autonomic nervous system abnormality such as OB/GYN conditions comprising administering an agent such as a beta blocker.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 1, 17, 33 of co-pending application No. 11/592,097.

Claims 1, 21 of the instant application teaches a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta blocker to treat conditions that include genitourinary conditions e.g renal failure etc.

Claims 1, 17, 33 of the co-pending application teach a method of treating a subject for autonomic dysfunction such as renal associated condition such as renal failure comprising administering a pharmacological agent, such as beta blocker, metoprolol.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the co-pending application teaches a method of treating autonomic nervous system abnormality such as renal associated condition comprising administering an agent such as metoprolol, a beta blocker.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 11-28, 41, 62-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims are directed to a method of treating a subject for a condition caused by an autonomic nervous system abnormality, said method comprising providing a subject known to suffer from an autonomic nervous system abnormality administering to said subject an effective amount of a beta blocker and the abnormality is selected from conditions including neurodegenerative conditions; neuroinflammatory conditions; orthopedic inflammatory conditions; lymphoproliferative conditions; autoimmune conditions; inflammatory conditions; infectious diseases, pulmonary conditions; transplant-related conditions, gastrointestinal conditions; endocrine conditions; genitourinary conditions selected from the group of renal failure, hyperreninemia, hepatorenal syndrome and pulmonary renal syndrome; aging associated conditions; neurologic conditions; Th-2 dominant conditions; conditions that cause hypoxia; conditions that cause hypercarbia; conditions that cause hypercapnia; conditions that cause acidosis; conditions that cause academia, pediatric-related conditions; OB-GYN conditions, sudden death syndromes, fibrosis; post-operative recovery conditions; post-procedural recovery conditions;

chronic pain; disorders of thermoregulation, cyclic vomiting syndrome and trauma. The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions. The specification in general teaches the dosage administration, routes, types of delivery, a list of beta blockers and non-beta blockers. The specification does not teach administration of a beta-blocker along with a non beta blocker to a subject known to suffer from an autonomic nervous system abnormality and treat such subjects for at least one of the conditions listed in claim 1. The specification does not provide data or show any examples of actual administration of beta blockers along with a non-beta blocking agent in conditions arising from autonomic nervous system abnormality. The scope of claim 23 is to use any beta blocker or any non-beta blocker agents in patients with one more conditions arising from autonomic nervous system abnormality. The specification does not give any specific guidance to age associated conditions resulting from abnormality of autonomic nervous system regarding (1) criteria for the dosages for specific age associated conditions (2) criteria for the counter indications in giving such beta blockers (3) criteria of dosage regimens for specific conditions e.g. when the dose needs to be administered, how many doses etc (4) criteria if patients suffer from multiple associated conditions. The patients can have multiple disease conditions and the therapy has to be patient specific and the conditions need to be monitored and it is not a trivial matter. Accordingly, the scope of the claims is broad. Also, the method claims comprise

administering a non-beta blocker (claims 23 and 24) in addition to administration of a beta-blocker. The specification has not given any guidance (1) in regards with counter indications of all the non-beta blockers claimed (2) the dosage amount to be provided with respect to age related conditions to make sure there are no adverse effects or the side effects are to a minimal (3) precautions in administration of drugs for patients with more than one condition. The specification does not provide adequate description and there are no specific examples to provide support to the claims. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not provide support to the subject matter of administration of a beta blocker and a non-beta blocking agent to a subject to treat the said subject for at least one of the conditions listed in claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims;

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and, (8) the quantity of experimentation necessary.

Claims 1, 3, 4, 11-28, 41, 62-71 are rejected under 35 U.S.C. 112, first paragraph, because the prior art, while being enabling for a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising administering an effective amount of at least one beta blocker to conditions like asthma, hypertension, glaucoma, migraine, anxiety disorders does not reasonably provide enablement for treating all the diseases or disorders listed in claim 1 with all the beta blockers and in combination with all non-beta blocking agents listed in claim 24. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

(1, 5) The nature of the invention and the breadth of the claims:

The instant claims are directed to a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising administering an effective amount of at least one beta-blocker to said subject to treat said subject for at least one of: neurodegenerative conditions; neuroinflammatory conditions; orthopedic inflammatory conditions; lymphoproliferative conditions; autoimmune conditions; inflammatory conditions; infectious diseases, pulmonary conditions; transplant-related conditions, gastrointestinal conditions; endocrine conditions; genitourinary conditions selected from the group of renal failure, hyperreninemia, hepatorenal syndrome and pulmonary renal syndrome; aging associated conditions; neurologic conditions; Th-2

dominant conditions; conditions that cause hypoxia; conditions that cause hypercarbia; conditions that cause hypercapnia; conditions that cause acidosis; conditions that cause academia, pediatric-related conditions; OB-GYN conditions, sudden death syndromes, fibrosis; post-operative recovery conditions; post-procedural recovery conditions; chronic pain; disorders of thermoregulation, cyclic vomiting syndrome and trauma. Claim 21 is limited to few beta blockers, claim 41 to few aging associated conditions. The claims are not limited to any dosage amounts. Claims 1, 3, 4, 11-20, 22-28, 62, 63 are very broad with respect to the conditions, number of beta blockers, to the dosage amounts and to a number of non-beta blocking agents (listed in claim 24).

(3) The relative skill of those in the art:

The relative skill of those in the pharmaceutical and medical arts is high, requiring advanced education and training.

(2) The state of the prior art:

Stockley (Are Beta blockers safe?, BMJ, 298, 10 Jun 1989) teaches that two patients developed cardiac failure upon administration of nifedipine (a calcium channel blocker, one of the non beta blockers claimed in claim 24 of the instant application) along with propranolol or atelenol or alprenolol (p 1584, para 2). Chester et al. (Chest 79, 5, May 1981) teaches adverse effects of propranolol on airway function in nonasthmatic chronic obstructive lung disease patients (see Abstract). Houston (Cardiol Clin, 1986, Feb 4(1), 117-35) teaches that several antihypertensive drugs have an adverse effect on glucose tolerance that may partially or completely negate the beneficial effects of reducing blood pressure as it relates to the incidence of coronary

heart disease and its complications and beta-blockers without intrinsic sympathomimetic activity have the greatest adverse effect on glucose intolerance. Liebermann et al. (Br J Obstet Gynaecol, 1978, 678-83, abstract) teaches that beta-adrenergic blockade is harmful to the hypoxic fetus, for these reasons the use of propranolol in hypertensive pregnancies complicated by placental insufficiency may be contraindicated unless there is no satisfactory alternative (See Abstract). Allen et al. teaches that there was an adverse effect of practolol, the occurrence of sinus bradycardia with or without an increase in the frequency of ventricular ectopic beats (See abstract). It has been well known in the prior art that beta blockers are useful in the treatment of angina, heart failure, high blood pressure, glaucoma and various disorders (http://en.wikipedia.org/wiki/Beta_blocker). Salpeter et al. (Cochrane Database of Systemic Reviews, 4, 2002) teach that beta blocker therapy has mortality benefits in patients with hypertension, heart failure, coronary artery disease as well as during the postoperative period (see Abstract). Also drugs that modulate adrenergic receptors such as beta blockers (e.g., metoprolol, atenolol) are known to cause inflammation to the joint (See Savola, BMJ, 287, 1983). In summary, the guidance from prior art is for the use of beta blockers in conditions like hypertension, heart failure, coronary artery disease as well as during the postoperative period, glaucoma etc, the adverse effects of certain beta blockers and the contraindications of beta blockers in combination with calcium channel blockers. The prior art or the specification does not teach that every single disease or disorder in the different classes of disorders (that are etiologically different) listed in claim 1 will be effectively treated by administration of the beta blockers (known and yet to be

discovered) nor does the prior art or specification teach that every combination of beta blocker with a non-beta blocking agent can be used without interactions and be effective in the treatment.

(4) The predictability of the art:

Despite the advance training of those in the art, the art is highly unpredictable. It is still not possible to predict the pharmacological activity or treatment efficacy of a compound based on the structure alone. It is also not possible to predict the efficacy of a given class of compounds for the treatment of a particular disease absent a mechanistic link between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Typically, in order to verify that a compound will be effective in treating a disease, the compounds must be either tested directly in a patient or in a model that has been established as being predictive of treatment efficacy. In order to predict whether a class of compounds would be effective in treating a disease, the etiology or pathophysiology of the disease must be uncovered, and there should be a nexus between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Absent experimental tests verifying the efficacy of a compound or a strong nexus between the known pharmacological activity of a class of agents and the etiology and/or pathophysiology of the condition, it is impossible to predict whether the compound or class of compounds (here beta blockers) would actually be effective for treating every single condition listed in clam 1. It is impossible to predict that every single beta blocker can be used in combination with every single non-beta blocker class of compounds listed in claim 24. It is impossible to

predict that every single beta blocker used in a method of treatment of condition caused by an autonomic nervous system abnormality will be effective in the treatment of every single disorder or disease in the different classes of disorders (that are etiologically different) listed in claim 1. Stockley (Are Beta blockers safe?, BMJ, 298, 10 Jun 1989) teaches that two patients developed cardiac failure upon administration of nifedipine (a calcium channel blocker, one of the non beta blockers claimed in claim 24 of the instant application) along with propranolol or atelenol or alprenolol (p 1584, para 2). Hence it is highly unpredictable what the outcome would be to due to the interaction of beta blockers with other drugs. Hence there is high unpredictability in the treatment of abnormal autonomic nervous disorders comprising administering a beta blocker with a non beta blocking agent. Chester et al. (Chest 79, 5, May 1981) teaches adverse effects of propranolol on airway function in nonasthmatic chronic obstructive lung disease patients (see Abstract). The unpredictability of the art is very high because there are hundreds of diseases listed in the claims of the instant application and a single disease or condition can be diagnosed via multiple biochemical pathways and treated via multiple biochemical pathways. The scope of enablement varies inversely with the degree of unpredictability of the factors involved, and physiological activity is generally considered to be unpredictable factor. There is a high degree of unpredictability involved in a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising administering an effective amount of at least one beta-blocker to said subject for all the diseases and disorders listed.

(6, 7) The amount of guidance presented and the presence of working examples:

It has been established that, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839 166 USPQ 18, 24 (CCPA 1970). The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions. There are no working examples provided in the specification in a method of treating a subject for an autonomic nervous system abnormality comprising providing an effective amount of a beta blocker to a subject to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. The specification does not teach administration of a beta-blocker to a subject to treat such subjects for at least one of the conditions listed in claim 1. There is no guidance in the specification with respect to the treatment of conditions with high parasympathetic activity with normal sympathetic activity. The specification does not provide specific examples to provide support to the claims. Also, there is a high degree of unpredictability involved in combining a beta blocker with a non-beta blocking drug as there may be drug interactions and if there are any adverse effects such combination may not be workable. In summary, Applicant has provided little guidance beyond what was recognized in the art at the time of filing.

(8) The quantity of experimentation needed:

In order to enable the instantly claimed methods commensurate with the entire scope, a large quantity of experimentation would be necessary. Disease states herein claimed do not flow from a single biochemical lesion, but form a range of physiological activities. The instant claimed maladies has no succinct etiological underpinnings, thus the recited conditions are not ameliorated by effecting a single biochemical lesion. That the instant maladies are not attributable to a single etiology, with the basis of the disease stated diffuse and multifaceted, the skilled artisan must teat each compound against the envisioned biochemical lesion to determine the possible use of such compounds in the instant invention. With Applicants' guidance provided in the specification and what is known in the prior art the person of ordinary skill in the art would have to conduct these experiments administering beta blockers for every single condition listed in claim 1 and with combination of non-beta blockers listed in claim 24. Considering the unpredictability of the combination of compounds due to their drug interactions, this would be an arduous and daunting task. It would require undue experimentation to test each beta blocker for all the conditions listed in a method of treating the subjects with autonomic nervous system abnormality. It would require undue experimentation to test each beta blocker with every single non beta blocking agent listed in claim 24 for every condition listed in a method of treating autonomic nervous system abnormality. It would require undue experimentation to test all beta blockers for every condition listed in claim 1 to produce at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Though the prior art has taught the use of certain beta blockers in conditions like heart disease, anxiety, hypertension etc it is not predictable from that data that every beta blocker would be useful in all the conditions listed namely, neurodegenerative conditions; neuroinflammatory conditions; orthopedic inflammatory conditions; lymphoproliferative conditions; autoimmune conditions; inflammatory conditions; infectious diseases, pulmonary conditions; transplant-related conditions, gastrointestinal conditions; endocrine conditions; genitourinary conditions selected from the group of renal failure, hyperreninemia, hepatorenal syndrome and pulmonary renal syndrome; aging associated conditions; neurologic conditions; Th-2 dominant conditions; conditions that cause hypoxia; conditions that cause hypercarbia; conditions that cause hypercapnia; conditions that cause acidosis; conditions that cause academia, pediatric-related conditions; OB-GYN conditions, sudden death syndromes, fibrosis; post-operative recovery conditions; post-procedural recovery conditions; chronic pain; disorders of thermoregulation, cyclic vomiting syndrome and trauma with the dosage amounts shown to be useful in specific conditions. Dosage depends on age, weight, pre-existing conditions, adverse effects, counter indications with drugs taken for other conditions etc. From the state of the prior art and from the guidance provided by the Applicants' it is not predictable that all the conditions listed in claim 1 when treated with beta blockers and a non-beta blocking agent would result in producing at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject Therefore, it would require undue, unpredictable experimentation to practice the claimed

invention of treating a subject for a condition caused by an autonomic nervous system abnormality comprising administering an effective amount of at least one beta-blocker to said subject to treat said subject for at least one of the conditions listed in claim 1 and to produce at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Gambardella et al. (Metabolism, 46, 3, March, 1999, p 291-297).

Gambardella et al. teach a method of treating a condition due to deficient parasympathetic activity associated with elevated basal metabolic rate in cancer patients by oral administration of propranolol (see Abstract, p 295, para 1, lines 1-8, p 296, para 4, 1-5). The reference teaches the autonomic nervous system dysfunction in cancer patients with elevated basal metabolic rate, there is an unbalanced sympathetic (SNS)/parasympathetic nervous system (PNS) ratio which may exist due to SNS over

activity in cancer patients due to impaired PNS activity. The reference further teaches that beta-blocker such as propranolol administration may be useful to counteract the negative impact of the SNS on metabolic pathways (p 297, para 3 continued on 298). Hence the reference inherently teaches the sympathetic bias in at least a portion of autonomic nervous system, abnormality characterized by sympathetic bias, parasympathetic bias with an unbalanced SNS/PNS ratio with high SNS activity and low PNS activity. In summary, Gambardella et al. teaches administration of a beta blocker such as propranolol in patients suffering from cancer to treat an autonomic nervous system abnormality (e.g. cancer, see Applicants' claim 41, cancer as one of the aging associated conditions caused by autonomic nervous system abnormality). The administration of a beta blocker (propranolol) to a cancer patient in a method of treating autonomic nervous system abnormality meets the structural limitation of the claim. Accordingly, the reference inherently teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Brevetti et al. (Brief communications, Nov 1981, p 938-941).

Brevetti et al. teach an intravenous and oral administration of propranolol for the treatment of Shy-Drager syndrome, a severe degeneration of the autonomic nervous system. The reference further teaches that orthostatic hypotension a condition of Shy-Drager syndrome is mainly dependent on peripheral vasodilation without the normal

response of postural vasoconstriction and may be a consequence of an imbalance of alpha and beta adrenoreceptor activity in peripheral nervous system and that beta-blockade may provide an effective means of treating orthostatic hypotension in patients with Shy-Drager syndrome (p 940 para 2, lines 1-5, continued on page 941). The reference teaches a sympathetic bias and a parasympathetic bias in at least a portion of said autonomic nervous system. In summary, Brevetti et al. teaches administration of a beta blocker such as propranolol in patients suffering from Shy-Drager syndrome an autonomic nervous system abnormality. The administration of a beta blocker (propranolol) to a Shy-Drager syndrome patient in a method of treating autonomic nervous system abnormality meets the structural limitation of the claim. Accordingly, the reference inherently teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Claims 1, 21, 23-25, 28, 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Davies et al. (The J of Intl Med Research, 1988, 16, 173-181).

Davies et al. teach the administration of ibuprofen, a non-steroidal anti-inflammatory drug along with an anti-hypertensive agent and a beta-blocker such as propranolol (see Abstract) to group of patients with hypertension. It is inherent that hypertension, an age-associated condition is common in elderly patients and parasympathetic nerves influence cerebral blood flow during hypertension. In summary, Davies et al. teaches administration of a beta blocker such as propranolol in patients

suffering from hypertension, an age associated condition, also an autonomic nervous system abnormality. Davies et al. in p 174, in Patients and Methods section teaches measuring blood pressure in patients and further teach that patients showing a clinically significant rise in blood pressure (>5 mm Hg) rise in diastolic blood pressure were eligible to continue. Accordingly, the reference teaches identification of a subject known to suffer from an autonomic nervous system disorder. The administration of a beta blocker (propranolol) to patient with hypertension in a method of treating autonomic nervous system abnormality meets the structural limitation of the claim. Accordingly, the reference inherently teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject.

Claims 1, 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Puskas (US 6,429,217).

Puskas teaches administration of a beta-adrenergic blocker (or a beta blocker such as propranolol) to a patient suffering from heart conditions (aging associated condition) and stimulation of one or both the vagus nerves (see col. 8, claim 1). In summary, Puskas teaches administration of a beta blocker such as propranolol in patients suffering from heart conditions, an age associated condition, also an autonomic nervous system abnormality. The administration of a beta blocker (propranolol) to patient with heart conditions in a method of treating autonomic nervous system abnormality meets the structural limitation of the claim. Accordingly, the reference

inherently teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject.

Claims 1, 16, 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Bugiardini et al. (Am J Cardiol, 1989, Feb 1, 63, 5, 286-90) as evidenced by Guilli et al. (Cardiovascular Research, 2001, 208-216).

Bugiardini et al. teach administration of propranolol to patients with X syndrome and further teach that the average number of ischemic episodes per 24 hours was significantly reduced during propranolol therapy compared with placebo (see abstract).

Guilli et al. teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity (see Abstract).

Bugiardini's teachings anticipate the claim of treating an autonomic nervous condition comprising administering beta propranolol because the reference teaches administration of a beta-blocker propanolol to patients with X-syndrome and Guilli et al. teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity. The administration of a beta blocker (propranolol) to patient with X-syndrome in a method of treating autonomic nervous system abnormality condition meets the structural limitation of the claim. Accordingly, the reference inherently teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the

parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject.

Claims 1, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Shimizu et al. (J of the Amer. College of Cardiology, 39, 12, June 2002) as evidenced by Morita et al. (Jpn Circ J 1996, Oct 60(10), 742-8).

Shimizu et al. in the abstract teaches the administration of propranolol to patients with LQT1 or LQT2 syndrome under normal sympathetic tone or during sympathetic stimulation.

Morita in the abstract teaches that The pathogenesis of LQTS and the induction of TdP have been thought to be closely related to autonomic nervous abnormalities and LQTS patients with TdP had lower abnormal sympathetic nervous activity than those without TdP

Shimizu et al's teachings anticipate the claim of treating an autonomic nervous abnormality condition because the reference teaches administration of a beta-blocker propanolol to patients with LQT-syndrome under normal tone or during sympathetic stimulation conditions and Morita et al. teaches that LQTS patients have autonomic nervous system abnormalities. Accordingly, the administration of a beta blocker (propranolol) to patient with LQT-syndrome meets the structural limitation of the claim of administering a beta blocker to a subject with autonomic nervous system abnormality. Accordingly, the reference inherently teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic

nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 63, 70, 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003) and Gambardella et al. (Metabolism, 46, 3, March, 1999, p 291-297) in view of Idekar et al. (U.S. 5,522854).

Lampert et al. teaches propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction patients (see Abstract, p 140, Discussion, para 1). Thus from the teachings of Gambardella et al. and Lampert et al. it is evident that parasympathetic activity is increased after propranolol administration with heart conditions. Lampert et al. teach administration of 180 or 240 mg/day of propranolol (See Methods).

Gambardella et al. teachings discussed as above.

It would have been obvious to one of ordinary skill in the art at the time of the invention that administration of a beta blocker such as propranolol increases the parasympathetic activity because of the teachings of Lampert et al. Lampert et al. teach that propranolol therapy improves recovery of parasympathetic tone in patients with

acute myocardial infarction patients. Hence by administration of same drug (as claimed), propranolol to patients would obviously have the same pharmacological effects such as increase in parasympathetic activity. The reference does not explicitly teach that administration of beta blockers produce parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject. However, Lampert et al. teach administration of propranolol 180 or 240 mg/day. The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence administration of the same compound with the suggested dosage amount (as in the specification of the instant application) to a subject with an autonomic nervous system abnormality condition would produce the same pharmacological effects of producing parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject.

The references do not teach determining the parasympathetic/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system.

Ideker et al. teaches that a preferred way to measure the ratio of sympathetic to parasympathetic nerve activity is to measure heart rate variability, as will be appreciated by those skilled in the art, with a decrease in heart rate variability indicating an increased risk of the onset of arrhythmia (col.3, lines 49-52).

It would have been obvious to one having ordinary skill in the art at the time of the invention to have measured the parasympathetic/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system from the teachings of Idekar et al. because the reference teaches a method to measure the ratio of sympathetic to parasympathetic nerve activity is to measure heart rate variability. One having ordinary skilled in the art at the time of the invention would have been motivated to determine the parasympathetic/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system is to use the ratio as an indicator to whether there is a decrease in heart rate variability that is associated with an increased risk of the onset of arrhythmia. It would have been obvious to one having ordinary skilled in the art to have used a beta blocker in response to the determined parasympathetic/sympathetic activity ratio because Lampert et al. teach the therapeutic benefits of administration of a beta blocker propranolol in patients with myocardial infarctions, an autonomic nervous system abnormality.

Claims 64-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March, 1999, p 291-297) as applied to claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62, 69 above in view of Mann et al. (US 2004/0147969, effective filing date 5/13/2003).

Gambardella et al. teachings discussed as above.

The references do not explicitly teach employing control feedback loop.

Mann et al. teaches therapeutic treatment for cardiac diseases comprising sensors. The reference further teaches that patients can be titrated to higher or more

appropriate beta-blocker dose levels with potentially increased survival benefits (see abstract, para 380) based on the signals.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann et al. One having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions. It would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensors in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol. The dosage administration is clearly a dose effective parameter that a person of ordinary skill in the art would routinely optimize. It would have been obvious to modulate the autonomic nervous system administering two different beta blocker protocols from the prior art teachings of Gamberdella, Mann et al, (para 321). From the teachings of Mann it would have been obvious to one of ordinary skill in the art to administer different doses or administer same or different beta blocker protocols in treating the disease conditions due to the modulation of autonomic nervous system from the output of the sensor signals and to produce parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the

parasympathetic activity /sympathetic activity ratio observed in a healthy 25 year old human subject.

Response to Arguments

1) *112(1) Written Description rejection*:

Applicants' argue that specific examples and doses are not necessary to provide an adequate written description of this novel approach of modulating autonomic function to treat multiple diseases, as the Office suggests". Applicants further argue that drugs in question are well known with known dosages and the specification provides adequate guidance.

Applicants' arguments filed 7/7/2009 stating the instant invention provide sufficient guidance and working examples are not required is fully considered but found not to be persuasive. The examiner does not dispute the fact that various beta blockers or non-beta blocking agents and the dosages are known in the literature. However, the claims of the instant invention are towards treating autonomic nervous system abnormality with beta blockers and additionally a non beta blocking agent. The claims are very broad with respect to all the beta blocking agents, non beta blocking agents and to the unrelated disorders that encompasses a vast array of neurodegenerative conditions, neuroinflammatory conditions; orthopedic inflammatory conditions; lymphoproliferative conditions; autoimmune conditions; inflammatory conditions; infectious diseases, pulmonary conditions; transplant-related conditions, gastrointestinal conditions; endocrine conditions; genitourinary conditions selected from the group of

renal failure, hyperreninemia, hepatorenal syndrome and pulmonary renal syndrome; aging associated conditions; neurologic conditions; Th-2 dominant conditions; conditions that cause hypoxia; conditions that cause hypercarbia; conditions that cause hypercapnia; conditions that cause acidosis; conditions that cause academia, pediatric-related conditions; OB-GYN conditions, sudden death syndromes, fibrosis; post-operative recovery conditions; post-procedural recovery conditions; chronic pain; disorders of thermoregulation, cyclic vomiting syndrome and trauma. The examiner is aware that the various disease states encompassed by the claims can be identified and treated. However, while it is known to identify different conditions and their treatments in the art, it is a totally different issue when one of skilled in the art attempts to treat all these seemingly art-recognized to be unrelated disorders with a single agent (beta blocker). Such concept is not known. And as admitted by the applicant this is the novelty of the instant invention. Since the concept is novel, the guidance required to enable one of skilled in the art would be significantly more. However, in the instant case, there is no sufficient guidance provided in the instant case of how different beta blockers would be used alone or with different beta blocking agents to treating all the conditions listed. The only nexus, according to the instant specification, for linking all the disorders encompassed by the claims is the parasympathetic/sympathetic activity, an autonomic nervous system abnormality. However, the examiner notes that there is no working example disclosed in the instant specification. It is not known in the art that all of the beta blockers and the entire non beta blocking agents disclosed in the instant specification would affect the autonomic nervous systems. Moreover, drugs that

modulate adrenergic receptors such as beta blockers (e.g., metoprolol, atenolol) are known to cause inflammation to the joint (See Savola, BMJ, 287, 1983). The specification has not given any guidance (1) in regards with counter indications of all the non-beta blockers claimed when administered along with a beta blocker (2) the dosage amount to be provided with respect to age related conditions to make sure there are no adverse effects or the side effects are to a minimal (3) precautions in administration of drugs for patients with more than one condition. Absent evidence to the contrary demonstrating a working invention, the instant claims are considered properly rejected under 35 USC 112, first paragraph.

2) *112(1) Enablement rejection*

Applicants' argue that "The inventors of the subject invention have formulated novel pharmacologic strategies to treat conditions including disease conditions by modulating autonomic function as the basis of therapy. Extensive support for this theory including multiple specific examples of diseases that can be treated along with references can be found in the specification, for example on p. 4, line 9 to p. 5, line 26, and p. 59, line 11 to p. 67, line 29". Applicants' further argue that treatment with beta blocking agents is well known in the art and directions for treatment can be found in the literature. In response, the specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions and in general teaches the dosage administration, routes, types of delivery, examples of

beta blockers and non-beta blockers. The specification however does not provide any other guidance or provide working examples for even one of the laundry list of disease conditions listed in claim 1. The claims encompass a vast array of disorders resulting from autonomic nervous system abnormality. The examiner notes that apparently, the applicant does not realize the broadness of the instant claims. The claims are so broad that they encompass a beta blocker and an addition non beta blocking agent in a method to treat all diseases listed. Furthermore, these different diseases encompass vastly diverse disorders that are well-recognized in the art having different etiologies. There is no working example disclosed in the instant specification that one single agent could treat all conditions. Even arguendo, the examiner clearly demonstrates that the full scope of the invention is not enabled because beta-blockers can cause joint inflammation according to Savola. Moreover, providing or listing all of the compounds do not mean providing "blaze marks", direction, and/or guidance to one of skilled in the art so that one of skilled in the art can practice the full scope of the invention without undue experimentation. The examiner further notes that although the compounds are individually well-known in the art, they are not well- known to be useful in treating the disorders claimed. The examiner does not dispute the fact that the various disease states encompassed by the claims can be identified and treated. However, while it is known to identify different conditions and their treatments in the art, it is a totally different issue when one of skilled in the art attempts to treat all these seemingly art-recognized to be unrelated disorders with a single agent. Such concept is not known. And as admitted by the applicant this is the novelty of the instant invention. Since the

concept is novel, the guidance required to enable one of skilled in the art would be significantly more. However, in the instant case, there is no sufficient guidance provided in the instant case. The only nexus, according to the instant specification, for linking all the disorders encompassed by the claims is the parasympathetic/sympathetic activity. However, the examiner notes that there is no working example disclosed in the instant specification. It is not known in the art that beta blocking agents and all of the non-beta blocking agents disclosed in the instant specification would affect the autonomic nervous systems. Moreover, drugs that modulate adrenergic receptors such as beta blockers (e.g., metoprolol, atenolol) are known to cause inflammation to the joint (See Savola). Although the method of the instant invention is not to discover specific compounds, it is to use these compounds to treat seemingly unrelated disorders. Taking the broadness of the claims, the lack of guidance in the specification, the state of the art, the predictability of the field, and the absence of the working example together, one of skilled in the art would have to perform undue experimentation to practice the full scope of the claims. The state of the art is that it is not known to use a single agent to treat all unrelated disorders listed in the claims. Absent evidence to the contrary demonstrating a working invention, the instant claims are considered properly rejected under 35 USC 112, first paragraph. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (Fed. Cir. 1997) states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and [p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of

general ideas that may or may not be workable". Accordingly, the claims are considered properly rejected under 35 USC 112, first paragraph.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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